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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/500,872	12/06/2004	Hubertus Johannes Marie Op Den Camp	28902.0008.	1317

30827 7590 11/29/2007

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EXAMINER	
FRONDA, CHRISTIAN L	
ART UNIT	**PAPER NUMBER**
1652	

MAIL DATE	DELIVERY MODE
11/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,872	OP DEN CAMP ET AL.	
	Examiner	Art Unit	
	Christian L. Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2007*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 6-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *06 December 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/704*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-4 and 6-24 are pending and under consideration in this Office Action.

2. The objection to the title of the invention as being not descriptive has been withdrawn in view of applicants' amendment to the title in the amendment filed 09/11/2007.

3. The previous grounds of rejection of claims 12-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement have been withdrawn in view of applicants' arguments and amendment to the claims in the amendment filed 09/11/2007.

4. The rejection of claims 1-4 and 6-20 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been withdrawn in view of the applicants' arguments and amendment to the claims in the amendment filed 09/11/2007.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4 and 6-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a cultured isolated eukaryotic cell transformed with a nucleic acid construct comprising a nucleotide sequence encoding a xylose isomerase comprising the amino acid sequence of SEQ ID NO: 1; and a process for producing ethanol, lactic acid, acetic acid, succinic acid, an amino acid, 1,3-propanediol, ethylene, glycerol, a β-lactam, or cephalosporin comprising fermenting a medium containing a source of xylose with the said eukaryotic cell; does not reasonably provide enablement any other embodiment as recited in the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The arguments filed 9/11/2007 have been fully considered but are not persuasive for reasons of record as further explained in detail below.

The nature and breadth of the amended claims encompass any cultured eukaryotic host cell transformed with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID

NO: 1.

It is well known in the prior art that the amino acid sequence of a protein determines the protein's structural and functional properties. Predictability of which changes can be tolerated in a protein's amino acid sequence to obtain a desired biological activity requires knowledge and guidance regarding specific amino acid residue(s) in the protein's amino acid sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification) and detailed knowledge of the protein's structure, and the ways in which the protein's structure relates to its function. The reference of Chica et al. (Curr Opin Biotechnol. 2005 Aug;16(4):378-84; PTO 892) teaches that the complexity of the structure/function relationship in enzymes has proven to be the factor limiting the general application of rational enzyme modification and design, where rational enzyme modification and design requires in-depth understanding of structure/function relationships.

The positions within a protein's amino acid sequence where modifications can be made with a reasonable expectation of success in obtaining a protein having the same biological activity are limited in any protein and the result of such modifications is highly unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g., multiple substitutions, deletions, additions, and combinations thereof.

Methods for isolating or generating variants and mutants using random mutagenesis techniques were known in the art. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the protein comprising an amino acid sequence of SEQ ID NO: 1 with an expectation of obtaining a protein having the same biological activity such as xylose isomerase activity. At the time of the invention, there was a high level of unpredictability associated with altering a protein sequence with an expectation that the protein will maintain the same desired biological activity. For example, the reference of Witkowski et al. (Biochemistry. 1999 Sep 7; 38(36): 11643-50; PTO 892) teaches that only a single amino acid substitution results in conversion of the activity of a protein to a second, distinct activity (see e.g., Table 1, page 11647). In addition, the reference of Seffernick et al. (J Bacteriol. 2001 Apr; 183 (8): 2405-10; PTO 892) teaches that two proteins with 98% amino acid sequence identity were found to catalyze different reactions, where one protein has melamine deaminase activity and the other protein has atrzine chlorohydrolase activity (see Fig.3, page 2408; **DISCUSSION** section on page 2409).

While methods of isolating and/or generating variants of a protein were known in the art at the time of the invention and the specification provides general teachings for searching and screening for the claimed invention, it was not routine in the art to screen by a trial and error process for all proteins having a substantial number of modifications as encompassed by the claims for those that maintain the same desired biological activity such as xylose isomerase activity.

Although the specification provides guidance and working example for an isolated polynucleotide from *Piromyces* sp. E2 (ATCC 76762) encoding a xylose isomerase consisting of

the amino acid sequence of SEQ ID NO: 1, yeast expression vectors containing said isolated polynucleotide, yeast host cells transformed with said expression vectors, and growth of said yeast host cells on xylose (see Examples 1-4); the specification does not provide guidance, working examples, or prediction for making any polynucleotide encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1. Although the xylose isomerases described in WO 04/99381 and WO 06/009434 has 97% and 83% identity to SEQ ID NO: 1, this does not provide guidance for altering SEQ ID NO: 1 with the expectation of attaining a protein that still retains xylose isomerase activity. Furthermore, the specification does not provide guidance, working examples, or prediction for making the genetic modifications recited in claims 7-11.

Thus, an undue amount of trial and error experimentation must be preformed where such experimentation involves searching and screening a vast number of biological sources for the claimed polynucleotide encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1. Alternatively, trial and error experimentation must then be performed to search and screen for specific amino acid residues in SEQ ID NO: 1 to change (e.g., amino acid deletion, insertion, substitution, and combinations thereof) which will not result in inactivation of xylose isomerase activity. General teaching regarding screening and searching for the claimed invention is not guidance for making the claimed invention.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific amino acid residues in SEQ ID NO: 1 which does not affect enzyme activity. Without such guidance, the amount of experimentation left to those skilled in the art to make the invention is undue and well outside of routine experimentation.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988).

Dependent claims 2-4 and 6-23 are included in the rejection because these claims do not correct the defect of claim 1.

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a

person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-4 and 21-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guan et al. (US Patent 5,643,758; published 07/01/1997; reference of record) or Karlsson et al. (Eur J Biochem. 2001 Dec;268(24):6498-507; reference of record) in view of Accession Q9P8C9 (published 2000-10-01; reference of record).

Guan et al. teach expression vectors containing promoters, prokaryotic host cells such as *E. coli* and eukaryotic host cells such as yeast, and methods for making, expressing, isolating, and purifying any protein fused to the *E.coli* maltose binding protein (MBP) using the said expression vectors, prokaryotic and eukaryotic host cells such as yeast; and that these methods and products are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques (see entire patent).

Karlsson et al. teach the filamentous fungus *Trichoderma reesei* host cell transformed with an expression vector containing a polynucleotide encoding Ce161A (EG IV) (see entire publication).

The teachings of Guan et al. and Karlsson et al. differs from the claims in that the yeast host cell or the filamentous fungus *Trichoderma reesei* host cell not transformed with a polynucleotide encoding a xylose isomerase comprising an amino acid sequence that has at least 70% , 80%, 90%, 95% identity to SEQ ID NO: 1 or is SEQ ID NO: 1.

Accession Q9P8C9 teach a xylose isomerase having an amino acid sequence that is 100% identical to SEQ ID NO: 1 (see attached alignment; reference of record).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use transform the yeast host cell taught by Guan et al. or *Trichoderma reesei* host cell taught by Karlsson et al. with the polynucleotide encoding the xylose isomerase taught by Accession Q9P8C9 having an amino acid sequence that is 100% identical to SEQ ID NO: 1. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to express and purify the xylose isomerase taught by Accession Q9P8C9. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because recombinant molecular biology techniques for heterologous or homologous expression of proteins is well developed in the art.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made, and was as a whole clearly *prima facie* obvious.

Applicants' arguments filed 09/11/2007 have been fully considered but are not

persuasive. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the claims as written do not specifically exclude recombinant protein expression since the claims clearly recite a cultured host cell transformed with a nucleic acid construct. One of ordinary skill in the art at the time the invention was made would have been motivated to combine the reference in the manner stated above in order to express and purify the xylose isomerase taught by Accession Q9P8C9. Furthermore, according to MPEP 2144 [R-5]:

> "It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Conclusion

9. No claim is allowed.

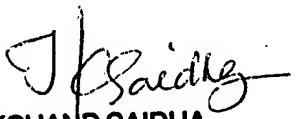
10. Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272 0929. The examiner can normally be reached Monday-Thursday and alternate Fridays between 9:00AM 6:30PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272 0928. The fax phone number for the organization where this application or proceeding is assigned is (571)273-8300.

12. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000. CLF



TEKCHAND SAIDHA
PRIMARY EXAMINER